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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/829,545	04/10/2001	Richard M. Weinshilbourn	07039-118002	8183

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EXAMINER

PROUTY, REBECCA E

ART UNIT	PAPER NUMBER
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1652

DATE MAILED: 04/23/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.
09/829,545

Applicant(s)
Weinshilboum et al.

Examiner
Rebecca Prouty

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on Jan 29, 2003
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 14-17, 32, and 34-37 is/are pending in the application.
- 4a) Of the above, claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 14-17, 32, and 34-37 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
*See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 9 6) ☐ Other:

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Claims 1-13, 18-31 and 33 have been canceled. Claims 14-17, 32, 34-36 and newly presented Claim 37 are at issue and are present for examination.

Claims 14-17, 32, 34-36 and 37 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 14-17, 32, 34-36 and 37 recite methods for determining a risk estimate of a cancer in a subject by detecting the presence of a sulfotransferase nucleotide sequence variant encoding a SULT1A1 polypeptide having a histidine at residue 213 and making a risk estimate based on the results. The specification and art each disclose that sulfonation of a wide variety of organic compounds with known or suspected connections to a variety of diseases is important to the bioactivity of these compounds, that a number of sulfotransferases are expressed in mammalian cells of which the encoding genes for many have been cloned, and that a number of polymorphisms of some these genes exist. However, the ability to determine the risk of any cancer, including a hormone dependent cancer from the presence or absence of a particular polymorphism require a clear knowledge of an established correlation between the presence/absence of a

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specific allele associated with the site detected and the presence of the disease. Such correlations are very difficult to establish in view of the extremely complex nature of the art. A wide variety of factors influence the development of cancers, including hormone-dependent cancers and these factors are not necessarily the same in every cancer nor are each of the factors of similar importance in each individual disease. Furthermore, different individuals may be exposed to different levels of potential carcinogens each of which may be influenced differently by altered levels of SULT1A1 activity such that the same individual could have an increased risk of a cancer induced by one carcinogen yet a decreased risk of the same cancer induced by other possible carcinogens. While sulfotransferases are clearly important enzymes in the bioactivity of many organic compounds, the effects of sulfonation may increase the activity or toxicity of some compounds and decrease the activity or toxicity of others. Sulfonation is a well known part of the degradation/elimination pathways of many potential carcinogens but also known to be important for the activation of other compounds. As such changes in activity of any sulfotransferase might have diverse effects on the development of cancers induced by different carcinogens and might increase the risk of one type of cancer while simultaneously decreasing the risk of another

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type of cancer. Furthermore, there are a large number of different sulfotransferase genes which are differently expressed in distinct tissue types and have sometimes overlapping and sometimes distinct substrate specificities such that a polymorphism which increased/decreased the activity of one sulfotransferase might have diverse effects on the development of cancer in different tissues depending of whether other sulfotransferases catalyzing the same reaction are present or absent in each of those tissues. Not only are there large numbers of different sulfotransferases, the presence/absence of many other enzymes involved in the bioactivation, degradation and/or elimination of any particular compound which can each have multiple different polymorphic forms further complicate the evaluation of the risk of any disease related to a particular compound and the correlation of changes in activity in any one enzyme to changes in the risk for the disease. For a good review of the knowledge of the prior art with regard to the influence of polymorphisms in sulfotransferases in cancer susceptibility see Hengstler et al.

The specification fails to teach that the presence of a histidine residue at amino acid 213 of SULT1A1 has a defined correlation to any particular cancer, including any hormone dependent cancer. While the specification discloses a difference

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in activity of the encoded sulfotransferase for the claimed polymorphism of SULT1A1, there is no showing that the differences in activity of the alleles correlates with an increased or decreased risk for even a single cancer, including any specific hormone dependent disease much less for **any** cancer. While the skilled artisan might expect that this polymorphism may be correlated with increased/decreased risk for some diseases, it would take undue experimentation to determine how this particular polymorphism correlates with such risk as the correlation may be different for distinct diseases as well as for distinct causes of even the same disease and the number of factors involved is immense. As such it would require undue experimentation for one to determine the risk of any cancer by determining the presence or absence of a sulfotransferase nucleotide sequence variant encoding a SULT1A1 polypeptide having a histidine at residue 213.

Applicants traverse this rejection by stating that the specification teaches that page 11, lines 14-17 state that patients having the SULT1A1*2 allele may have an increased risk of developing breast cancer and that page 32, lines 3-10 state that patients with malignant hepatic disease had higher levels of SULT1A1 activity than patients with benign disease. Applicants further cite the references of Vachon et al., Zheng et al. and Wu

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et al. in support of enablement of the claims. First it should be noted that each of Vachon et al., Zheng et al. and Wu et al. was published after the filing date of the instant application. Enablement must be present as of the filing date of the claimed invention. As such the disclosures of Vachon et al., Zheng et al. and Wu et al. can not be relied on to show enablement of the instant invention.

Page 11, lines 14-17 of the specification provide nothing more than a blanket statement that a subject having a SULT1A1*2 allele **may** have a greater risk of having breast cancer. There is **no** data to support this statement. For all the reasons discussed above one of skill in the art would not find this unsupported statement sufficient as to how to assess the risk of **any** cancer, or even any breast cancer based on the presence or absence of the SULT1A1*2 allele as this allele may be either protective or increase the risk of cancers induced by different carcinogens.

While page 32, lines 3-10 state that patients with malignant hepatic disease had higher levels of SULT1A1 activity than patients with benign disease, the total number of patients involved is only 7 with no disclosure as the potential distinctions in these patients with regard to other known factors which influence cancer risk. As the sample size is so small, and

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other factors are not controlled for, the skilled artisan would not find this data to be sufficient evidence to support an assertion even that risk of hepatic malignancy could be assessed by determining the presence or absence of the SULT1A1*2 allele much less the risk of **any** cancer as claimed.

Further evidence of lack of enablement of the instant claims comes directly from Wu et al. cited by applicants which clearly show that the art is far from clear that there is a direct correlation between SULT1A1 genotype and any cancer even as of the 2002 publication date of Wu et al. which is substantially after applicants filing date. Wu et al. state:

"Three epidemiological studies about the association of SULT1A1 and malignancy **have not been conclusive**. In one study, a lack of association between this polymorphism and prostate cancer was noted in 134 cases and 184 controls. Two large-scale studies have investigated the effect of this polymorphism on breast cancer risk in women. Although Zheng et al. found his/his to be an independent risk factor for breast cancer in women, Seth et al. did not. All 3 studied Caucasian populations. Carlini et al. reported a wide racial variation in SULT1A1 polymorphism." (page 101),

"It is apparent that further investigation is required to clarify the effect of SULT1A1 polymorphism on cancer risk." (page 103),

"SULT1A1 bioactivates and detoxifies endogenous and exogenous compounds such as phenolic xenobiotics, iodothyronines and hydroxylated aromatic amines. The precise way that SULT1A1 influences cancer development and **whether certain SULT1A1 genotypes predispose to cancer are not clear at this time**." (page 103),

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"Because the relationship between environmental carcinogens and esophageal cancer risk is complicated, the effect of SULT1A1 on sexual hormones and on environmental carcinogens needs further study." (page 103), and

"Because this is an association study, it is possible that the frequency of SULT1A1 polymorphism may be in linkage disequilibrium with other potential important polymorphisms for the risk of esophageal cancer." (pages 103-104).

Each of the above quotes make it clear that even though the data collected by Wu et al. suggested that the presence of the SULT1A1*2 allele correlates to an increased risk of esophageal cancer in Asians, that they do not consider the data they collected conclusive that this is in fact the case and clearly believe it is insufficient to support a conclusion that the presence of the SULT1A1*2 allele correlates to an increased risk of **any** cancer as claimed. Furthermore, while applicants presented 3 studies (all conducted after the filing date of the instant application) which suggest some correlation of the presence of the SULT1A1*2 allele to an increased risk of a cancer, the art contains other studies which suggest no such correlation exists. See for example Seth et al. which showed no correlation of breast cancer risk to SULT1A1 genotype, directly opposite to the results of Zheng et al. and Wong et al. and Steiner et al. which showed no correlation of colorectal and

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prostate cancer risk, respectively, to SULT1A1 genotype. Furthermore, Ozawa et al. suggest that for urothelial cancer, the presence of the SULT1A1*1 allele, in combination with a specific allele of N-acetyltransferase 2 (NAT2) may increase cancer risk, although the influence of the sulfotransferase genotype is far from clear and not statistically significant alone. Other studies such as that of Bamber et al. provide data suggesting that the SULT1A1*1 allele is associated with a reduced risk of colorectal cancer in some instances (patients under 80) but increased risk in other instances (patients over 80).

All of the above references, make it clear that even long after the filing date of the instant application, that it would require undue experimentation for the skilled artisan to determine the risk of any cancer or even any specific type of cancer based on the presence or absence of a histidine residue at position 213 of the SULT1A1 protein.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is

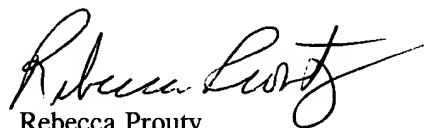
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not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rebecca Prouty, Ph.D. whose telephone number is (703) 308-4000. The examiner can normally be reached on Monday-Friday from 8:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy, can be reached at (703) 308-3804. The fax phone number for this Group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.



Rebecca Prouty
Primary Examiner
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